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THE ROLE OF BACTERIAL INFECTIONS IN SEVERITY OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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ХУЛОСА

Сурункали обструктив ўпка касаллиги (СОЎК) симптомларни ёмонлаштирадиган ва касалликнинг ривожланишига ёрдам берадиган такрорланувчи бактериал инфекциялар билан боғлиқ. Ушбу тадқиқотнинг мақсади СОЎК билан оғриган беморларда бактериал инфекцияларнинг тарқалишини ва уларнинг ҳаво оқимининг чекланиши ва яллиғланиш маркерлари билан боғлиқлигини аниқлаш. Тадқиқотимизда СОЎК билан оғриган 140 нафар бемор ва 110 нафар соғлом шахслар назоратда бўлдилар. Бактериал патогенларни аниқлаш учун балғам намуналари экилди, ўпка функционал ҳолатини аниқлаш тестлари ўтказилди ва артериал қонда газлар таркиби аниқланди. ИФА таҳлили ёрдамида интерлейкин-8 (ИЛ-8) миқдори аниқланди. СОЎК билан оғриган беморларда Haemophilus influenzae, Streptococcus pneumoniae ва Moraxella catarrhalis нинг тарқалиши назорат гуруҳига қараганда анча юқори бўлди. Бактериал юк ва ИЛ-8 миқдори ўртасида ижобий боғлиқлик аниқланди, айниқса ҳаво оқимининг қаттиқроқ чеклови бўлган беморларда (FEV1 < 35%). Бактериал инфекциялар ва ИЛ-8 юқори миқдорлари СОЎКнинг оғир кечиши билан кучли боғлиқ бўлиши, касаллик қайталаниш даражасини камайтириш учун мақсадли аралашувлар зарурлигини кўрсатади.

Калит сўзлар: *СОЎК, бактериал инфекциялар, ҳаво оқимининг чекланиши, ИЛ-8, яллиғланиш.*

РЕЗЮМЕ

Хроническая обструктивная болезнь легких (ХОБЛ) ассоциируется с рецидивирующими бактериальными инфекциями, которые усугубляют симптомы и способствуют прогрессированию заболевания. Целью данного исследования было изучение распространенности бактериальных инфекций у пациентов с ХОБЛ и их взаимосвязи с ограничением воздушного потока и маркерами воспаления. Было проведено перекрестное исследование 140 пациентов с ХОБЛ и 110 здоровых лиц. Образцы мокроты культивировались для выявления бактериальных патогенов, проводились функциональные пробы легких и измерялись газы артериальной крови. Уровень интерлейкина-8 (ИЛ-8) в сыворотке крови определяли с помощью ИФА. У пациентов с ХОБЛ была значительно выше распространенность Haemophilusinfluenzae, Streptococcuspneumoniae и Moraxellacatarrhalis по сравнению с контрольной группой. Была выявлена положительная корреляция между бактериальной нагрузкой и уровнем IL-8, особенно у пациентов с более выраженным ограничением воздушного потока (FEV1 < 35%). Бактериальные инфекции и повышенныйуровень ИЛ-8 тесно связаны с тяжелой формой ХОБЛ, что указывает на необходимость целенаправленных мероприятий по снижению частоты обострений.

Ключевые слова: *ХОБЛ, бактериальные инфекции, ограничение воздушного потока, ИЛ-8, воспаление.*

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a leading cause of morbidity and mortality worldwide, particularly in older adults and individuals with a history of smoking [3,7]. Characterized by persistent respiratory symptoms and airflow limitation, COPD is a progressive condition that encompasses a spectrum of pathophysiological changes, including chronic bronchitis, emphysema, and small airway disease. The Global Burden of Disease Study has identified COPD as the third leading cause of death globally, with exacerbations significantly contributing to both disease progression and healthcare costs [1,3].

One of the hallmarks of COPD is its association with recurrent bacterial infections, which play a critical role in the exacerbation of symptoms and the decline in lung function. Frequent exacerbations not only increase the risk of hospitalization but also lead to faster disease progression and poorer overall outcomes [2-4]. Among the bacterial pathogens commonly implicated in COPD exacerbations are Haemophilus influenzae, Streptococcus pneumoniae, and Moraxella catarrhalis. The colonization of the lower respiratory tract by these bacteria is a key driver of inflammation, which further contributes to the worsening of airflow limitation and pulmonary function in COPD patients [4,8,11].

Emerging evidence suggests that the degree of bacterial colonization and the specific bacterial species present may be closely linked to the severity of COPD. For instance, patients with severe airflow obstruction, as measured by Forced Expiratory Volume in one second (FEV1), are more likely to harbor potentially pathogenic bacteria in their airways compared to those with milder forms of the disease. Furthermore, the presence of bac-

terial infections in COPD patients has been associated with elevated levels of pro-inflammatory cytokines, particularly interleukin-8 (IL-8), which is known to recruit neutrophils to the site of infection and amplify the inflammatory response [5,7,9].

The interplay between bacterial infections and inflammation in COPD underscores the importance of identifying key bacterial pathogens and understanding their impact on disease progression. While several studies have demonstrated a relationship between bacterial colonization and COPD exacerbations, there remains a need for further investigation into the prevalence of specific bacterial species in relation to the severity of airflow limitation and inflammatory marker levels [8].

THIS STUDY AIMS to address this gap by examining the prevalence of bacterial infections in COPD patients compared to a control group of healthy individuals. Furthermore, the study investigates the correlation between bacterial load, severity of airflow limitation, and levels of IL-8 in COPD patients. By exploring these relationships, the study seeks to provide insights into the role of bacterial infections in COPD pathogenesis and identify potential targets for therapeutic interventions aimed at reducing exacerbations and slowing disease progression.

MATERIALS AND METHODS

Study Design and Population

This was a cross-sectional observational study conducted between 2020 and 2023in the laboratory of immunoregulation of the Institute of Human Immunology and Genomics of the Academy of Sciences of the Republic of Uzbekistan.The study included a total of 250 participants, consisting of 140 patients diagnosed with Chronic Obstructive Pulmonary Disease (COPD) and 110 healthy individuals serving as a control group. COPD patients were recruited from [hospital/clinic], with diagnoses confirmed according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines based on clinical symptoms and pulmonary function test results. The control group was composed of age- and sex-matched individuals without any known pulmonary or systemic disease.

Inclusion and Exclusion Criteria

Inclusion Criteria:

- Patients aged between 48 and 82 years.
- Diagnosed with moderate to severe COPD based on spirometry results (FEV1 < 50% of the predicted value).
- Current or former smokers with a history of at least 10 pack-years of smoking.

Exclusion Criteria:

- Patients with asthma, interstitial lung disease, or any other chronic lung diseases.
- Those with an active infection or taking immunosuppressive medication.
- Pregnant women or patients with a history of malignancies.

Ethical Considerations

The study protocol was reviewed and approved by the Ethics Committee of [Institution], and written informed consent was obtained from all participants in accordance with the Declaration of Helsinki.

Data Collection

Baseline Characteristics: Demographic data, smoking status, and pack years of smoking were recorded for all participants. Pulmonary function was assessed using spirometry, with key measurements including Forced Expiratory Volume in one second (FEV1) and Forced Vital Capacity (FVC). Arterial blood gases were analyzed to determine partial pressure of oxygen (PaO2) and partial pressure of carbon dioxide (PaCO2).

Microbiological Analysis

Sputum samples were collected from all participants, including both spontaneous expectoration in COPD patients and induced sputum in the control group. Samples were immediately transported to the laboratory and processed for bacterial culture within two hours of collection.

Bacterial Identification: Bacterial cultures were performed on blood agar, chocolate agar, and MacConkey agar plates. The plates were incubated at 37°C in a 5% CO2 atmosphere for 24–48 hours. Standard microbiological techniques, including Gram staining, catalase, and oxidase tests, were employed to identify bacterial species. The presence of Haemophilus influenzae, Streptococcus pneumoniae, Moraxella catarrhalis, and Pseudomonas aeruginosa, among other pathogens, was determined.

Pulmonary Function Testing

Pulmonary function tests were conducted using a [spirometer model], following the American Thoracic Society (ATS) guidelines. FEV1, FVC, and the FEV1/FVC ratio were recorded. Airflow limitation was categorized as mild, moderate, or severe based on FEV1 values. The severity of airflow obstruction was classified according to GOLD stages as follows:

- GOLD 1: FEV1 ≥ 80% predicted
- GOLD 2: FEV1 50-79% predicted
- GOLD 3: FEV1 30-49% predicted
- GOLD 4: FEV1 < 30% predicted

Inflammatory Marker Measurement

Serum levels of interleukin-8 (IL-8) were measured using enzyme-linked immunosorbent assay (ELISA) kits (manufacturer) according to the manufacturer's protocol. The correlation between IL-8 levels and bacterial load was analyzed using regression analysis.

Statistical Analysis

Data were analyzed using SPSS version [X.X]. Continuous variables were expressed as mean ± standard deviation (SD), while categorical variables were presented as frequencies and percentages. Comparisons between groups were made using the chi-square test for categorical variables and the Wilcoxon-U test for continuous variables. A p-value of less than 0.05 was considered statistically significant.

The association between bacterial colonization, severity of COPD (based on FEV1 values), and inflammatory markers was evaluated through linear regression

analysis. An R^2 value of 0.59 was used to assess the strength of the relationship between IL-8 levels and bacterial load.

RESULTS

The table 1 compares the baseline characteristics of COPD patients (n=140) and a control group (n=110), including demographic details, smoking status, pulmonary function test results, and other health-related measures.

Table 1

Baseline Characteristics of COPD Patients and Control Group

Characteristic	COPD Patients (n=140)	Control Group (n=110)	p-value
Males	90 (64.3%)	65 (59.1%)	p>0.05
Females	50 (35.7%)	45 (40.9%)	p>0.05
No (%) current smokers	85 (61%)	20 (18%)	p<0.001
Mean (range) age (years)	66 (48-82)	64 (47-80)	N/A
FEV1 (L)	1.13±0.2	2.54±0.3	p<0.0001
FEV1 (% predicted)	47.9±15.3	93.3±5.5	p<0.0001
FEV1/FVC (% predicted)	35.6±10.2	81.6±5.7	p<0.0001
PaO2 (kPa)	8.48±0.7	12.42±0.5	p<0.0001
PaCO2 (kPa)	6.18±0.5	4.92±0.3	p<0.0001
Pack years of smoking	63.0±15.0	5.5±3.0	p<0.0001
Daily inhaled steroid dosage (mg)	1.4+0.5	N/A	N/A
Note: Statistical analysis was performed using chi-square and Wilcoxon-U tests. A p-value of<0.05 was considered statistically significant.			

The proportion of males among COPD patients was 64.3% (90 individuals), compared to 59.1% (65 individuals) in the control group ($p > 0.05$), while females made up 35.7% (50 individuals) of the COPD group and 40.9% (45 individuals) of the control group ($p > 0.05$). These findings suggest no significant difference in gender distribution between the two groups.

In terms of smoking status, 61% of COPD patients (85 individuals) were current smokers, a stark contrast to only 18% (20 individuals) in the control group ($p<0.001$). The difference in smoking history between the two groups is evident from the pack years of smoking, with COPD patients having a mean of 63.0±15.0 pack years, compared to just 5.5±3.0 in the control group ($p<0.0001$).

The pulmonary function test results demonstrate a significant difference between the two groups. COPD patients had a lower mean FEV1 (Forced Expiratory Volume in one second) of 1.13±0.2 liters, whereas the control group had 2.54±0.3 liters ($p<0.0001$). Similarly, the percentage of predicted FEV1 was markedly lower in COPD patients (47.9±15.3%) compared to the control group (93.3±5.5%) ($p<0.0001$). Additionally, the FEV1/FVC (Forced Vital Capacity) ratio was significantly lower in the COPD group (35.6±10.2%) compared to the control group (81.6±5.7%) ($p<0.0001$), reflecting impaired lung function in COPD patients.

Table 2

Prevalence of Bacterial Infections in COPD Patients and Control Group

Bacterialinfection	COPD Patients	Control Group	p-valuecategory
Haemophilusinfluenzae	75 (53.6%)	10 (9.1%)	p<0.0001
Streptococcus pneumoniae	46 (32.9%)	15 (13.6%)	p<0.001
Moraxellacatarrhalis	28 (20.0%)	8 (7.3%)	p<0.01
Pseudomonasaeruginosa	15 (10.7%)	2 (1.8%)	p<0.01
Haemophilusparainfluenzae	25 (17.9%)	3 (2.7%)	p<0.0001
Staphylococcusaureus	18 (12.9%)	6 (5.5%)	p>0.05
Klebsiellapneumoniae	12 (8.6%)	4 (3.6%)	p>0.05
Escherichiacoli	9 (6.4%)	5 (4.5%)	p>0.05
Enterobacterspp.	7 (5.0%)	3 (2.7%)	p>0.05
Mycoplasmapneumoniae	5 (3.6%)	3 (2.7%)	p>0.05
No bacterialinfectiondetected	18(12.9%)	69(62.7%)	p<0.001
Note: Statistical analysis was performed using chi-square tests. A p-value of<0.05 was considered statistically significant.			

Arterial blood gas measurements also showed notable differences between the two groups. COPD patients had a lower mean PaO2 (partial pressure of oxygen) of 8.48±0.7 kPa, compared to 12.42±0.5 kPa in the control

group (p<0.0001). Conversely, the mean PaCO2 (partial pressure of carbon dioxide) was elevated in COPD patients (6.18±0.5 kPa) compared to the control group (4.92±0.3 kPa) (p<0.0001), indicating respiratory compromise in COPD patients.Lastly, while daily inhaled steroid dosage was reported for COPD patients (1.4 mg), this data was not available for the control group.

The table 2 presents a comparative analysis of bacterial infections between COPD patients and a control group, highlighting the prevalence of various bacteria in each group.

The most prevalent bacterial infection in COPD patients was Haemophilus influenzae, found in 75 patients (53.6%), while it was detected in only 10 individuals (9.1%) in the control group (p<0.0001). This suggests that H. influenzae plays a significant role in COPD exacerbations or infections. Similarly, Streptococcus pneumoniae was detected in 46 COPD patients (32.9%) compared to 15 in the control group (13.6%) (p<0.001), indicating its higher prevalence in COPD patients.

Moraxella catarrhalis was found in 28 COPD patients (20.0%), compared to 8 individuals (7.3%) in the control group (p<0.01), showing an increased frequency among those with COPD. Additionally, Pseudomonas aeruginosa was present in 15 COPD patients (10.7%) and only 2 control individuals (1.8%) (p<0.01), pointing to its higher association with COPD. The bacterium Haemophilusparainfluenzae was found in 25 COPD patients (17.9%) and in 3 individuals from the control group (2.7%) (p<0.0001), further illustrating its role in COPD-related infections.

In contrast, the prevalence of Staphylococcus aureus in COPD patients was 18 (12.9%) compared to 6 (5.5%) in the control group (p > 0.05), indicating no significant difference between the two groups. Similarly, Klebsiella pneumoniae was detected in 12 COPD patients (8.6%) and 4 individuals in the control group (3.6%) (p > 0.05), and Escherichia coli was present in 9 COPD patients (6.4%) and 5 in the control group (4.5%) (p > 0.05), neither showing substantial variation in their occurrence.

Additionally, Enterobacter spp. was found in 7 COPD patients (5.0%) and 3 control group individuals (2.7%) (p > 0.05), and Mycoplasma pneumoniae was detected in 5 COPD patients (3.6%) and 3 control participants (2.7%) (p > 0.05), again with no noteworthy difference between the two groups. Lastly, the control group had 69 individuals without bacterial infection, but no data is provided for the number of COPD patients without bacterial infection.

Overall, the data indicates that certain bacteria, such as Haemophilus influenzae and Streptococcus pneumoniae, are more prevalent in COPD patients, whereas others do not differ significantly between the two groups.

The table 3 compares the prevalence of bacterial infections in COPD patients based on the severity of airflow limitation, categorized by FEV1 (Forced Expiratory Volume in one second) values. The two groups consist of patients with FEV1<35% (n=70), representing more severe airflow limitation, and those with FEV1 > 35% (n=70), indicating relatively better lung function.

Table 3

Prevalence of Bacterial Infections in COPD Patients with FEV1<35% and FEV1 > 35%

Bacteria	FEV1<35% (n=70)	FEV1 > 35% (n=70)	P-values
Haemophilusinfluenzae	40 (57%)	15 (21%)	p<0.001
Streptococcus pneumoniae	30 (43%)	16 (23%)	p<0.01
Moraxellacatarrhalis	20 (29%)	8 (11%)	p<0.01
Pseudomonasaeruginosa	12 (17%)	3 (4%)	p<0.05
Haemophilusparainfluenzae	15 (21%)	10 (14%)	p ≥ 0.05
Staphylococcusaureus	10 (14%)	5 (7%)	p ≥ 0.05
Klebsiellapneumoniae	8 (11%)	4 (6%)	p ≥ 0.05
Escherichiacoli	5 (7%)	5 (7%)	p ≥ 0.05
Enterobacterspp.	3 (4%)	4 (6%)	p ≥ 0.05
Mycoplasmapneumoniae	3 (4%)	2 (3%)	p ≥ 0.05
No bacterialinfectiondetected	12 (17%)	40 (57%)	p<0.01
Note: Statistical analysis was performed using chi-square tests. A p-valueof<0.05 wasconsideredsta tisticallysignificant.			

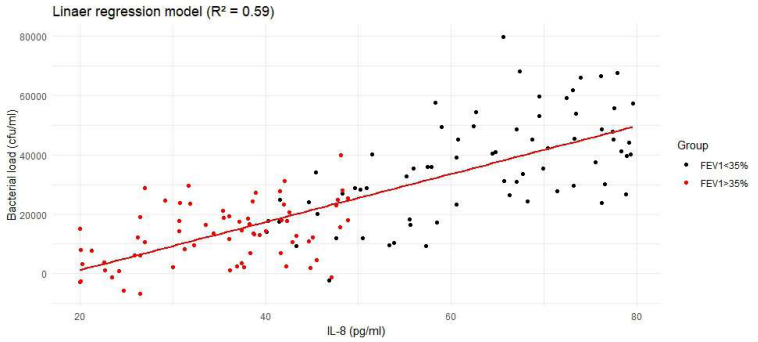
Haemophilus influenzae was detected in 57% (40 individuals) of the patients with FEV1<35%, whereas it was present in only 21% (15 individuals) of those with FEV1 > 35% (p<0.001), indicating a higher prevalence in the group with more severe airflow limitation. Similarly, Streptococcus pneumoniae was found in 43% (30 individuals) of patients with FEV1<35%, compared to 23% (16 individuals) in the FEV1 > 35% group (p<0.01). These findings suggest a significant association between decreased lung function and the presence of these bacterial pathogens.

Moraxella catarrhalis was more frequently identified in patients with FEV1<35%, where 29% (20 individuals) were positive, compared to 11% (8 individuals) in the FEV1 > 35% group (p<0.01). Pseudomonas aeruginosa followed a similar trend, being present in 17% (12 individuals) of patients with FEV1<35%, compared to only 4% (3 individuals) in the FEV1 > 35% group (p<0.05).

Forotherbacteria,suchasHaemophilusparainfluenzae (21% vs. 14%, p ≥ 0.05), Staphylococcus aureus (14% vs. 7%, p ≥ 0.05), Klebsiella pneumoniae (11% vs. 6%, p ≥ 0.05), and Escherichia coli (7% in both groups, p ≥ 0.05),

no significant differences were observed between the two groups. Similarly, there was no statistically significant variation for Enterobacter spp. (4% vs. 6%, $p \geq 0.05$) and Mycoplasma pneumoniae (4% vs. 3%, $p \geq 0.05$).

Interestingly, the proportion of patients with no bacterial infection was significantly higher in the FEV1 > 35% group, with 57% (40 individuals) showing no bacterial presence, compared to only 17% (12 individuals) in the FEV1<35% group ($p<0.01$).



Pic. 1. Correlation Between IL-8 Levels and Bacterial Load in COPD Patients.

The graph 1 demonstrates a positive linear relationship between IL-8 levels and bacterial load in COPD patients, with an R^2 value of 0.59. This indicates that higher levels of IL-8 are associated with an increased bacterial load. Patients with more severe airflow limitation (FEV1 < 35%, represented by black points) tend to have both higher IL-8 levels and higher bacterial loads compared to those with FEV1 > 35% (red points). The clustering of data suggests that patients with worse lung function are more likely to experience elevated bacterial colonization, potentially due to an exaggerated inflammatory response, as indicated by increased IL-8 levels. This trend is consistent across both groups, though the correlation is particularly evident in the more severely affected group.

DISCUSSION

The study highlights the significantly higher prevalence of Haemophilus influenzae and Streptococcus pneumoniae in COPD patients compared to the control group. The increased detection of these bacteria in patients with severe COPD, as indicated by their low FEV1 values, suggests that the impaired lung function in these individuals may predispose them to bacterial colonization and infection. This aligns with existing literature, which identifies these pathogens as key contributors to COPD exacerbations and disease progression [3,13].

Further, the presence of Moraxella catarrhalis and Pseudomonas aeruginosa in a higher proportion of patients with more severe COPD indicates that these bacteria, while less prevalent overall, are associated with more advanced stages of the disease. The detection of Pseudomonas aeruginosa in particular, a pathogen known for its role in chronic lung infections, underscores the vulnerability of patients with severely reduced lung function to opportunistic infections [3-5,12].

Interestingly, no significant difference was observed in the prevalence of other bacteria such as Staphylococcus aureus, Klebsiella pneumoniae, and Escherichia coli between COPD patients and the control group, as well as between patients with varying degrees of lung impairment. This suggests that while these bacteria may colonize the respiratory tract in COPD patients, they are less strongly associated with the severity of airflow limitation compared to other pathogens [2,7,14].

The linear regression analysis demonstrating a positive correlation between IL-8 levels and bacterial load further supports the hypothesis that bacterial colonization in COPD patients is linked to an inflammatory response. IL-8, a pro-inflammatory cytokine, is known to play a key role in neutrophil recruitment to the lungs, which may exacerbate tissue damage and perpetuate the cycle of inflammation and infection. The R^2 value of 0.59 indicates a moderate to strong relationship between IL-8 levels and bacterial load, particularly in patients with more severe airflow limitation (FEV1 < 35%). This finding suggests that IL-8 could be a useful biomarker for identifying patients at higher risk of bacterial infections and disease exacerbations [13,14].

Lastly, the significantly higher proportion of patients with no bacterial infection in the group with better lung function (FEV1 > 35%) reinforces the protective role of relatively preserved lung function in reducing the risk of bacterial colonization. This finding underscores the importance of early intervention and management strategies aimed at preserving lung function in COPD patients to mitigate the risk of recurrent infections and exacerbations [9-13].

CONCLUSIONS

This study demonstrates that bacterial infections, particularly with Haemophilus influenzae, Streptococcus pneumoniae, and Moraxella catarrhalis, are significantly more prevalent in patients with Chronic Obstructive Pulmonary Disease (COPD) compared to healthy individuals. The presence of these bacterial pathogens is closely associated with more severe airflow limitation, as indicated by lower FEV1 values, especially in patients with FEV1 < 35%. Furthermore, a positive correlation between bacterial load and interleukin-8 (IL-8) levels highlights the role of inflammation in COPD pathogenesis.

The findings suggest that bacterial colonization and

elevated inflammatory markers such as IL-8 contribute to the worsening of lung function and disease progression in COPD patients. Additionally, the significantly higher proportion of patients without bacterial infections in those with better-preserved lung function underscores the importance of early intervention to prevent exacerbations.

These results emphasize the need for targeted therapeutic interventions aimed at reducing bacterial infections and controlling inflammation to improve clinical outcomes in COPD patients. Future research should focus on the development of strategies to mitigate the impact of bacterial colonization and inflammation in the management of COPD.

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